IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Patent Application No. 10/802,220

Confirmation No. 3562

Applicant: Sunami et al.

Filed: March 17, 2004

TC/AU: 1614

Examiner: Pagonakis, A.

Docket No.: 227833

Customer No.: 23460

APPELLANTS' APPEAL BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In support of the appeal from the final rejection dated October 15, 2008, Appellants now submit their Brief.

Real Party In Interest

The patent application that is the subject of this appeal is assigned to Japan Tobacco Inc.

Related Appeals and Interferences

There are no appeals or interferences that are related to this appeal.

Status of Claims

The status of the claims is set forth in the Appendix attached hereto. Claims 1-8 and 15-23 are currently pending and are the subject of this appeal.

Status of Amendments

No amendments were filed by Appellants subsequent to the final rejection dated October 15, 2008. All prior amendments have been entered by the Office.

Summary of Claimed Subject Matter

Claims 1-8 and 15-23 are under examination. Claims 1-8 are directed to a pharmaceutical composition, and claims 15-23 are directed to a method of treating a cardiovascular disorder.

More specifically, independent claim 1, from which claims 2-4 are dependent, is directed to a pharmaceutical composition comprising (i) *S*-[2-([[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino)phenyl] 2-methylpropanethioate (hereinafter "JTT-705") and (ii) crospovidone (see, e.g., page 3, lines 5-8, page 19, lines 9-26, and page 25, lines 13-14, of the specification (i.e., paragraphs 0015, 0075, and 0089)). Independent claim 5, from which claims 6-8 are dependent, is directed to a pharmaceutical composition comprising (i) a substantially crystalline cholesteryl ester transfer protein (hereinafter "CETP") inhibitor, wherein the amount of inhibitor in amorphous form does not exceed about 10%, and (ii) a water-insoluble concentration-enhancing additive, wherein the CETP inhibitor is JTT-705 (see, e.g., page 3, lines 5-8, page 19, lines 9-26, and page 22, line 28, through page 23, line 9, of the specification (i.e., paragraphs 0015, 0075, and 0079)). Dependent claims 15-23 are directed to a method of treating a cardiovascular disorder with the pharmaceutical composition of independent claim 1 (see, e.g., page 28, line 30, through page 29, line 8, of the specification (i.e., paragraph 0101)).

All citations to the specification are to the substitute specification filed with the Office on October 8, 2004.

Grounds of Rejection to be Reviewed on Appeal

A. Whether claims 1-8 and 15-23 are unpatentable under 35 U.S.C. § 103(a) in view of Gumkowski et al. (U.S. Patent Application Publication 2006/0014788) in combination with Ault et al. (U.S. Patent 7,049,283) and Englert et al. (U.S. Patent 6,723,751).

B. Whether claims 1-8 and 15-23 are unpatentable for nonstatutory obviousness-type double patenting over claims 1-24 of Shinkai et al. II (U.S. Patent 6,753,346) in view of Ault et al. (U.S. Patent 7,049,283).

Argument

A. Obviousness Rejection

The subject matter defined by claims 1-8 and 15-23 allegedly is obvious in view of Gumkowski et al. in combination with Ault et al. and Englert et al.

The appealed claims define a pharmaceutical composition comprising JTT-705 and crospovidone (claims 1-4), as well as a pharmaceutical composition comprising (i) a substantially crystalline JTT-705, wherein the amount of JTT-705 in amorphous form does not exceed about 10%, and (ii) a water-insoluble concentration-enhancing additive (claims 5-8). Each of claims 2-8 requires a crystallinity feature. In particular, claim 2 requires that more than 50% of JTT-705 is crystalline, claims 4 and 6 require that JTT-705 is crystalline, and claims 3, 5, 7, and 8 require that JTT-705 is substantially crystalline such that the amorphous form does not exceed about 10%. The appealed claims also define a method of treating a cardiovascular disorder with a pharmaceutical composition comprising JTT-705 and crospovidone (claims 15-23).

For subject matter defined by a claim to be considered obvious, the Office must demonstrate that the differences between the claimed subject matter and the prior art "are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a); see also *Graham v. John Deere Co.*, 383 U.S. 1, 148 U.S.P.Q. 459 (1966). The ultimate determination of whether an invention is or is not obvious is based on certain factual inquiries including: (1) the scope and content of the prior art, (2) the level of ordinary skill in the prior art, (3) the differences between the claimed invention and the prior art, and (4) objective evidence of nonobviousness. *Graham*, 383 U.S. at 17-18, 148 U.S.P.Q. at 467.

1. Scope and Content of the Prior Art

Gumkowski et al. discloses self-emulsifying pharmaceutical compositions that are liquid solutions, suspensions, and oil-in-water emulsions. The compositions comprise a CETP inhibitor (one of many examples of which is JTT-705), and other co-solvents, surfactants, and optionally a digestible oil. Gumkowski et al. discloses the administration of the self-emulsifying pharmaceutical compositions in encapsulated dosage forms such as soft or hard gelatin capsules or aqueous oral emulsions formed by addition to water or another aqueous liquid. The compositions reportedly provide enhanced bioavailability because of

increased concentrations of CETP inhibitors. Gumkowski et al. further discloses the administration of the pharmaceutical compositions to raise high density lipoprotein (HDL), lower low density lipoprotein (LDL), and to treat atherosclerosis.

Ault et al. discloses a solid pharmaceutical composition for oral delivery comprising an active agent, crospovidone or povidone, and a delivery agent for the active agent. Ault et al. also discloses solid pharmaceutical compositions comprising calcitonin and either crospovidone or povidone. Ault et al. reportedly describes that the composition comprising crospovidone versus compositions without crospovidone provided enhanced bioavailability of calcitonin (col. 9, lines 34-38).

Englert et al. discloses crystalline (i.e., polymorphic) forms of the sodium salt of 5-chloro-2-methoxy-N-(2-(4-methoxy-3-methylaminothiocarbonylaminosulfonylphenyl)ethyl) benzamide and preparations, compositions, and use thereof. The compound of Englert et al. inhibits ATP-sensitive potassium channels and can be used to treat ischemic conditions of the heart.

2. Level of Ordinary Skill in the Art

For the purposes of the present appeal, one of ordinary skill in the art can be treated as someone with an advanced degree in chemistry or biology and/or at least a few years of experience in the pharmaceutical field.

3. Differences Between Claimed Invention and Prior Art

Gumkowski et al. discloses *hundreds* of disparate CETP inhibitors – only one of which is JTT-705 (see paragraphs 0113-1035). Gumkowski et al. does not contain any disclosure that singles out JTT-705, which is required by all of the appealed claims, from among the numerous other CETP inhibitors disclosed therein. In addition, Gumkowski et al. does not teach or suggest a composition comprising crospovidone, as required by product claims 1-4 and 8 and method claims 15-23. Moreover, Gumkowski et al. does not disclose the crystalline or amorphous form of the CETP inhibitor, as required by product claims 2-8. Gumkowski et al. discloses that the self-emulsifying formulations contain "no visibly detectable crystallization of CETP inhibitor" (paragraphs 0036, 0037, and 1060). The Examiner contends that Gumkowski et al. discloses that the CETP inhibitor can be provided in a formulation in an amount of 1-50 wt%, which meets the limitation requiring that more than 50% of the CETP inhibitor is crystalline as required by claim 2 (Office Action dated October 15, 2008, page 5, second paragraph). However, Gumkowski et al.'s disclosure that *a*

composition can include a CETP inhibitor *in an amount of 1-50 wt%* clearly does not mean that more than 50% of the CETP inhibitor is *crystalline*, as required by claim 2.

Neither Ault et al. nor Englert et al. discloses JTT-705, which is required by all of the appealed claims. Indeed, while Ault et al. discloses the use of crospovidone, Ault et al. is not directed to the use of CETP inhibitors *at all* or even the treatment of cardiovascular disorders. Similarly, Englert et al. is not directed to the use of CETP inhibitors *at all*. Furthermore, Englert et al. discloses the crystallization of a single benzamide compound. A benzamide moiety is based on the structure phenyl-C(O)-NH_2, in which the phenyl ring is attached to the carbonyl of an amide moiety. In contrast, JTT-705 does not include a benzamide structure because, as shown below, JTT-705 does not contain a moiety based on phenyl-C(O)-NH_2. In other words, the chemical structure of the compound of Englert et al. is quite different from that of JTT-705.

4. Objective Evidence of Unobviousness

For purposes of the present appeal, Appellants have no need to refer to any objective evidence of unobviousness of the present invention as defined by the appealed claims.

5. Consideration of Graham Factors Together

To compensate for the deficiencies of Gumkowski et al. vis-à-vis the subject matter defined by the appealed claims, the Examiner relies upon Ault et al. and Englert et al. In short, the Examiner ignores the fact that Gumkowski et al. discloses *hundreds* of disparate CETP inhibitors – only one of which is JTT-705 – and then takes the position that it would have been obvious for one of ordinary skill in the art to (a) utilize the crospovidone of Ault et al. in the composition of Gumkowski et al. because crospovidone provided enhanced bioavailability of a different and structurally unrelated active agent disclosed in Ault et al., and (b) use the crystallization techniques disclosed in Englert et al. for a different and structurally unrelated compound to provide a crystalline form of JTT-705 to use in the composition of Gumkowski et al.

As the Supreme Court recently stated, "*there must be some articulated reasoning* with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 127 S. Ct. 1727, 1741, 82 U.S.P.Q.2d 1385, 1396 (2007) (emphasis added)). See also *In re* Kotzab, 217 F.3d 1365, 1371, 55 U.S.P.Q.2d 1313 (Fed. Cir. 2000) ("Particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.");

In re Rouffet, 149 F.3d 1350, 1357, 47 U.S.P.Q.2d 1453 (Fed. Cir. 1998) ("In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.").

With respect to the present application, however, the Examiner has failed to articulate credible reasons to support her position that one of ordinary skill in the art would have combined the disclosures of Gumkowski et al., Ault et al., and Englert et al. so as to provide the present invention as defined by the appealed claims.

First, the Examiner has failed to articulate any reason for one of ordinary skill in the art to select JTT-705 from among the *hundreds* of disparate CETP inhibitors disclosed in Gumkowski et al.

Second, while the Examiner has alleged that one of ordinary skill in the art would have considered utilizing crospovidone in the composition of Gumkowski et al. because crospovidone provided enhanced bioavailability of the active agent disclosed in Ault et al., the Examiner provides no credible rationale for her belief that one of ordinary skill in the art would have even consulted the disclosure of Ault et al. in the course of preparing a composition of Gumkowski et al., let alone that one of ordinary skill in the art would have reasonably considered that the utilization of crospovidone in the composition of Gumkowski et al. would have had any beneficial effect on that composition. Indeed, since Gumkowski et al. pertains to compositions containing CETP inhibitors for use in the treatment of cardiovascular disorders, whereas Ault et al. is not directed to the use of *any* CETP inhibitors or even the treatment of cardiovascular disorders, one of ordinary skill in the art would have had *no reason* to even consider the disclosure of Ault et al. in preparing a composition of Gumkowski et al.

Third, while the Examiner has alleged that one of ordinary skill in the art would have considered adding a crystalline CETP inhibitor, especially JTT-705, in the composition of Gumkowski et al. because Englert et al. happens to disclose the crystallization of a benzamide compound, the Examiner provides no credible rationale for her belief that one of ordinary skill in the art would have even consulted the disclosure of Englert et al. in the course of preparing a composition of Gumkowski et al., let alone that one of ordinary skill in the art would have reasonably considered that a crystalline CETP inhibitor, especially JTT-705, in the composition of Gumkowski et al. would have had any beneficial effect on that

composition. Indeed, since Gumkowski et al. pertains to compositions containing CETP inhibitors for use in the treatment of cardiovascular disorders, while Englert et al. is not directed to the use of *any* CETP inhibitors, and Englert et al. pertains to the crystallization of a compound with a chemical structure that is quite different from that of JTT-705, one of ordinary skill in the art would have had *no reason* to even consider the disclosure of Englert et al. in preparing a composition of Gumkowski et al.

In view of the unrelatedness of the disclosures of Gumkowski et al., Ault et al., and Englert et al., one of ordinary skill in the art would have considered combining the disclosures of Gumkowski et al., Ault et al., and Englert et al. *only* with the hindsight knowledge of Appellants' invention. However, it is improper and impermissible to utilize hindsight knowledge of an invention in considering whether and how the disclosures of cited references are considered in evaluating the patentability of the invention. See, e.g., *In re Dembiczak*, 175 F.3d 994, 999, 50 U.S.P.Q.2d 1614, 1617 (Fed. Cir. 1999) ("Measuring a claimed invention against the standard established by section 103 requires the oft-difficult but critical step of casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field."); see also *W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1553, 220 U.S.P.Q. 303, 313 (Fed. Cir. 1983) (warning of the danger of "fall[ing] victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher").

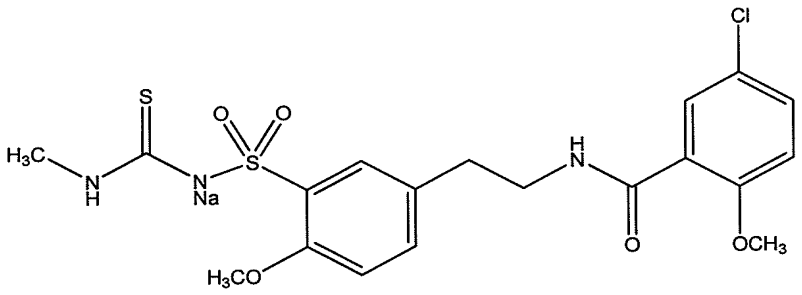
Even if one of ordinary skill in the art would have consulted Ault et al. and Englert et al. in preparing a composition of Gumkowski et al., one of ordinary skill in the art would not have considered modifying the composition of Gumkowski et al. in accordance with any teachings of Ault et al. and/or Englert et al. and would have had no reasonable expectation that such modifications would be successful.

Since Ault et al. is not directed to the use of *any* CETP inhibitors or even the treatment of cardiovascular disorders, one of ordinary skill in the art would have had no reason to even try using the crospovidone disclosed in Ault et al. in a CETP inhibitor-containing composition of Gumkowski et al. and would have had no reasonable belief that crospovidone would have any beneficial effect on a CETP inhibitor-containing composition of Gumkowski et al.

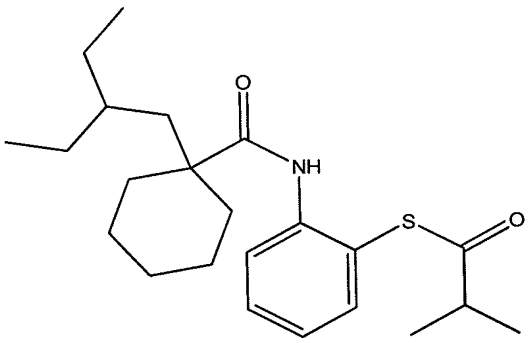
Moreover, Gumkowski et al. discloses self-emulsifying pharmaceutical compositions that are liquid solutions, suspensions, and oil-in-water emulsions, whereas Ault et al. discloses a solid pharmaceutical composition. Gumkowski et al. discloses preparing a CETP-inhibitor-containing pre-concentrate that forms a stable emulsion when mixed with water or other aqueous medium. The stable emulsion is then used to fill a softgel capsule (paragraph 0031). Gumkowski et al. does not teach the use of a solid formulation, such as a tablet. Therefore, one of ordinary skill in the art would not have been led by the disclosure of Ault et al. to use crospovidone in the self-emulsifying pharmaceutical compositions of Gumkowski et al. because Ault et al. discloses the use of crospovidone only in a solid pharmaceutical composition. In addition, the Examiner has not articulated any credible reason as to why one of ordinary skill in the art would have reasonably believed that crospovidone could be successfully used in the significantly different self-emulsifying compositions of Gumkowski et al.

Similarly, since Englert et al. is not directed to the use of *any* CETP inhibitors, but rather pertains to the crystallization of a single compound with a chemical structure that is quite different from that of JTT-705, one of ordinary skill in the art would have had no reason to even try crystallizing the CETP inhibitor, especially JTT-705, and adding it to a composition of Gumkowski et al. and would have had no reasonable belief that such crystallization would have any beneficial effect on a CETP inhibitor-containing, especially a JTT-705-containing, composition of Gumkowski et al.

In particular, Englert et al. discloses the crystallization of the sodium salt of a single compound that includes a benzamide moiety. The compound of Englert et al. and JTT-705, as set forth in a listing of possible CETP inhibitors in Gumkowski et al., are quite unrelated to one another, as is immediately apparent by a consideration of the structures of the compounds, which are set forth below for convenience.



Englert et al.



JTT-705

As discussed above, the compound of Englert et al. has a benzamide functional group, whereas JTT-705 does *not* have a benzamide functional group (i.e., phenyl-C(O)-NH_2). Instead, the group to which Appellants believe the Examiner is referring to in JTT-705 is an N-phenyl cyclohexylcarboxamide group. The Examiner maintains that "given that the crystallization of benzamides (as stated above [in Englert et al.]) is capable one would also be motivated to crystallize *any* benzamide" (Office Action dated October 15, 2008, page 4, bottom paragraph, emphasis added). Even if true, however, this statement is inapposite to the present situation inasmuch as JTT-705 does not contain a benzamide moiety and, therefore, is not "a benzamide." In addition, the compound of Englert et al. and JTT-705 include several other functional groups that are not common to the two compounds (e.g., sulfonyl and thiourea). In view of the overall unrelatedness of the chemical structures of the compound of Englert et al. and JTT-705, one of ordinary skill in the art would not have reasonably believed that the crystallization technique disclosed in Englert et al. could or should be applied with success to JTT-705.

Moreover, given the desired properties of the self-emulsifying formulation disclosed by Gumkowski et al., one of ordinary skill in the art would be led away from preparing a self-emulsifying formulation comprising a crystalline CETP inhibitor. In particular, Gumkowski

et al. teaches that a self-emulsifying formulation is "stable for at least several (i.e., for at least 6) hours, meaning there is no visibly detectable phase separation and that there is no visibly detectable crystallization of CETP inhibitor" (paragraph 0036). In the examples of Gumkowski et al., the stability of a self-emulsifying formulation is determined by the lack of crystalline CETP inhibitor in the composition (see, e.g., paragraph 1060). Gumkowski et al. teaches against the use of a crystalline CETP inhibitor because "[s]uspensions of crystalline drug do not provide sufficient concentrations of drug in solution due to very low aqueous solubilities and therefore yield inadequate blood levels." (paragraph 0010). As a result, even if it were assumed that one of ordinary skill in the art would knowingly select JTT-705 from among the hundreds of CETP inhibitors listed in Gumkowski et al., one of ordinary skill would not have consulted Englert et al. for teachings on how to prepare a crystalline compound, since Gumkowski et al. clearly teaches away from using a crystalline CETP inhibitor in the formulation disclosed therein.

Further, even if one of ordinary skill in the art were to believe that, based on the disclosure of Englert et al., JTT-705 could and should be crystallized and added to a composition of Gumkowski et al., one of ordinary skill in the art would not have arrived at the specific crystallinity features required by claims 2-8. In particular, nothing in Englert et al. teaches or suggests providing JTT-705 in a *specific* crystalline or amorphous amount (i.e., claim 2 requires that more than 50% of JTT-705 is crystalline, claims 4 and 6 require that JTT-705 is crystalline, and claims 3, 5, 7, and 8 require that JTT-705 is substantially crystalline such that the amorphous form does not exceed about 10%). Indeed, Englert et al. does not disclose or suggest *any* specific level of crystalline and/or amorphous product in a composition, let alone the specifically claimed amounts required by claims 2-8.

In view of the foregoing, Appellants maintain that the Examiner has failed to establish a *prima facie* case of obviousness over the combination of Gumkowski et al., Ault et al., and Englert et al., and that the present invention is unobvious over the combination of the cited references. Accordingly, Appellants submit that the obviousness rejection should be reversed.

B. Obviousness-type Double Patenting Rejection

Claims 1-8 and 15-23 have been rejected for nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 1-24 of Shinkai et al. II in view of Ault et al.

An obviousness-type double patenting rejection is only proper when the pending claims of an application recite an obvious variation of the invention that is *claimed* in a patent or patent application (MPEP § 804.II.B.1). The *specification* of the relied upon patent or patent application – here, Shinkai et al. II – is not involved in such an analysis. However, contrary to this standard, the Examiner states, "[i]t is obvious from the above teachings of [the Shinkai et al. II] '346 patent that it expressly contemplates variation in the dosage amounts and schedule of the active agents" (Office Action dated October 15, 2008, page 7, first full paragraph). Appellants note that, while the *specification* of Shinkai et al. II discloses administration information about JTT-705, the *claims* of Shinkai et al. II do not "expressly contemplate variation in dosage amounts and schedule of the active agents."

Shinkai et al. II contains *claims* directed to JTT-705, a composition thereof, as well as a method of inhibiting CETP activity, a method of increasing HDL, a method of decreasing LDL, a method of treating or preventing atherosclerosis, and a method of treating or preventing hyperlipidemia. The *claims* of Shinkai et al. II do not teach or suggest (a) a pharmaceutical composition comprising JTT-705 *and crospovidone* (e.g., claims 1-4), (b) a pharmaceutical composition comprising (i) substantially crystalline JTT-705, in which the amount of inhibitor in amorphous form does not exceed about 10%, and (ii) *a water-insoluble concentration-enhancing additive* (e.g., claims 5-8), or (c) a method for the treatment of a cardiovascular disorder by administration of a pharmaceutical composition comprising JTT-705 *and crospovidone* (e.g., claims 15-23), as required by the appealed pending claims.

Since the *claims* of Shinkai et al. II do not teach or suggest a pharmaceutical composition comprising a water-insoluble concentration-enhancing additive, such as crospovidone, the Examiner relies on the disclosure of Ault et al. However, upon considering the *claims* of Shinkai et al. II, one of ordinary skill in the art would not know that there existed a need to increase the bioavailability of JTT-705 and as such would *not* know to seek another reference, let alone specifically Ault et al., which is *not* directed to the use of CETP inhibitors at all or the treatment of cardiovascular disorders, i.e., the subject matter of the claims of Shinkai et al. II.

Moreover, since Ault et al. is not directed to the use of *any* CETP inhibitors or even the treatment of cardiovascular disorders, Ault et al. does not provide any credible reason as to why one of ordinary skill in the art would have even tried using crospovidone in a composition of Shinkai et al. II. Ault et al. also does not provide a basis for a reasonable belief that crospovidone could be successfully used to increase the bioavailability of JTT-

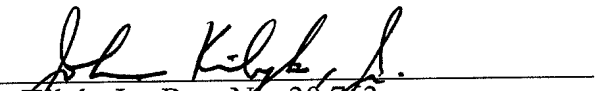
705. Given the unrelatedness of the subject matter of the claims of Shinkai et al. II and the disclosure of Ault et al., it is only with the benefit of hindsight knowledge of Appellants' invention that one might argue that one of ordinary skill in the art would have considered combining the subject matter of the claims of Shinkai et al. II and the disclosure of Ault et al. in the manner alleged by the Examiner.

In view of the foregoing, the Examiner has failed to establish a *prima facie* case of obviousness-type double patenting. Accordingly, the subject matter of the appealed claims is unobvious in view of the claims of Shinkai et al. II and the disclosure of Ault et al., and the obviousness-type double patenting rejection should be reversed.

Conclusion

For the foregoing reasons, Appellants respectfully request the reversal of the obviousness rejections of the subject patent application.

Respectfully submitted,



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Date: June 15, 2009

Claims Appendix

1. (Previously Presented) A pharmaceutical composition comprising (i) a cholesteryl ester transfer protein inhibitor that is *S*-[2-([[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino)phenyl] 2-methylpropanethioate and (ii) crospovidone.

2. (Previously Presented) The pharmaceutical composition of claim 1, wherein more than 50% of the cholesteryl ester transfer protein inhibitor is crystalline.

3. (Previously Presented) The pharmaceutical composition of claim 1, wherein the cholesteryl ester transfer protein inhibitor is substantially crystalline, wherein the amount of inhibitor in amorphous form does not exceed about 10%.

4. (Previously Presented) The pharmaceutical composition of claim 1, wherein the cholesteryl ester transfer protein inhibitor is crystalline.

5. (Previously Presented) A pharmaceutical composition comprising (i) a substantially crystalline cholesteryl ester transfer protein inhibitor, wherein the amount of inhibitor in amorphous form does not exceed about 10% and (ii) a water-insoluble concentration-enhancing additive,

wherein the cholesteryl ester transfer protein inhibitor is *S*-[2-([[1-(2-ethylbutyl)cyclohexyl]carbonyl]amino)phenyl] 2-methylpropanethioate.

6. (Original) The composition of claim 5, wherein the cholesterol ester transfer protein inhibitor is crystalline.

7. (Original) The composition of claim 5, wherein the cholesterol ester transfer protein inhibitor and water-insoluble concentration-enhancing additive are in a weight ratio of about 2:1 to about 9:1.

8. (Original) The composition of claim 7, wherein the water-insoluble concentration-enhancing additive is crospovidone.

9.-14. (Canceled)

15. (Previously Presented) A method for the treatment of a cardiovascular disorder in a mammal, which comprises administering to the mammal a therapeutically effective amount of a pharmaceutical composition of claim 1.

16. (Original) The method of claim 15, wherein the cardiovascular disorder is selected from the group consisting of atherosclerosis, peripheral vascular disease, dyslipidemia, hyperbetalipoproteinemia, hypoalphalipoproteinemia, hypercholesterolemia, hypertriglyceridemia, familial-hypercholesterolemia, angina, ischemia, cardiac ischemia, stroke, myocardial infarction, reperfusion injury, angioplastic restenosis, hypertension, and vascular complications of diabetes, obesity or endotoxemia.

17. (Original) The method of claim 15, wherein the cardiovascular disorder is selected from the group consisting of cardiovascular disease, coronary heart disease, coronary artery disease, hypoalphalipoproteinemia, hyperbetalipoproteinemia, hypercholesterolemia, hyperlipidemia, atherosclerosis, hypertension, hypertriglyceridemia, hyperlipidoproteinemia, peripheral vascular disease, angina, ischemia, and myocardial infarction.

18. (Previously Presented) The method of claim 15, wherein a maximum concentration of the cholesteryl ester transfer protein inhibitor, or active form thereof, in the bloodstream of a mammal is at least about 0.35 μg/mL post-treatment relative to pretreatment when the cholesteryl ester transfer protein inhibitor is administered at a daily dose of 600 mg with food.

19. (Previously Presented) The method of claim 15, wherein a maximum concentration of the cholesteryl ester transfer protein inhibitor, or active form thereof, in the bloodstream of a mammal is at least about 0.8 μg/mL post-treatment relative to pretreatment when the cholesteryl ester transfer protein inhibitor is administered at a daily dose of 900 mg with food.

20. (Previously Presented) The method of claim 15, wherein an area under the plasma concentration-time curve $AUC_{0-\infty}$ of the cholesteryl ester transfer protein inhibitor, or active form thereof, in the bloodstream of a mammal is at least about 3.5 μg·h/mL post-treatment relative to pretreatment when the cholesteryl ester transfer protein inhibitor is administered at a daily dose of 600 mg with food.

21. (Previously Presented) The method of claim 15, wherein an area under the plasma concentration-time curve $AUC_{0-\infty}$ of the cholesteryl ester transfer protein inhibitor, or active form thereof, in the bloodstream of a mammal is at least about 7.5 μg·h/mL post treatment relative to pretreatment when the cholesteryl ester transfer protein inhibitor is administered at a daily dose of 900 mg with food.

22. (Previously Presented) The method of claim 15, wherein cholesteryl ester transfer protein activity in the bloodstream of a mammal is inhibited post-treatment by at least about 25% relative to CETP activity pretreatment when the cholesteryl ester transfer protein inhibitor is administered at a daily dose of 600 mg with food.

23. (Previously Presented) The method of claim 15, wherein cholesteryl ester transfer protein activity in the bloodstream of a mammal is inhibited post-treatment by at least about 35% relative to CETP activity pretreatment when the cholesteryl ester transfer protein inhibitor is administered at a daily dose of 900 mg with food.

Evidence Appendix

None

Related Proceedings Appendix

None